

ATTORNEY DOCKET NO. 112911.01701

PATENT

CLAIMS

1. (Original) A synthetic tetrapeptide that binds an Inhibitor of Apoptosis Protein (IAP) and relieves IAP-mediated inhibition of caspase activity, wherein the tetrapeptide binds a surface groove within a BIR domain of the IAP.
2. (Original) The synthetic tetrapeptide of claim 1, wherein the BIR domain is a BIR 2 domain or a BIR3 domain.
3. (Original) The synthetic tetrapeptide of claim 1, having an amino acid sequence the same as an N-terminal sequence of a cellular IAP-binding protein.
4. (Original) The synthetic tetrapeptide of claim 3, wherein the cellular IAP-binding protein is a mammalian protein or a Drosophila protein.
5. (Original) The synthetic tetrapeptide of claim 1, having a sequence X1-X2-X3-X4 (SEQ ID NO:29), wherein

X1 is A

X2 is V, T or I,

X3 is P or A, and

X4 is F, Y, I or V.

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6. (Original) The synthetic tetrapeptide of claim 5, selected from the group consisting of AVPI (SEQ ID NO:1), AVAF (SEQ ID NO:2); AIAY (SEQ ID NO:3), AVPF (SEQ ID NO:4), ATPF (SEQ ID NO:5), AVPY (SEQ ID NO:6) and ATPV (SEQ ID NO:7).

7. (Original) The synthetic tetrapeptide of claim 6, which is AVPF (SEQ ID NO:4).

Composite
4-7

8. (Original) A synthetic peptide that binds IAP and relieves IAP-mediated inhibition of caspase activity, comprising the tetrapeptide of claim 1 and a C-terminal extension of one or more of up to three additional amino acid residues comprising a sequence the same as a sequence of a cellular IAP-binding protein in residues 5-7 of its N-terminus.

9. (Original) The synthetic peptide of claim 8, selected from the group consisting of:
 - (i) a pentapeptide wherein the C-terminal amino acid is Y or F;
 - (ii) a hexapeptide comprising the pentapeptide of (i) and a C-terminal amino acid which is L or I;
 - (iii) a heptapeptide comprising the hexapeptide of (ii) and a C-terminal P.

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10. (Original) The synthetic peptide of claim 9, having a sequence selected from the group consisting of AVAFYIP (SEQ ID NO:9), AIAYFLP (SEQ ID NO:10) and AVPFYLP (SEQ ID NO:11).
11. (Original) A non-peptide or partial peptide mimetic of the synthetic tetrapeptide of claim 3.
12. (Original) A non-peptide or partial peptide mimetic of the synthetic peptide of claim 8.
13. (Original) A method of stimulating apoptosis in a cell, comprising administering to the cell the synthetic tetrapeptide of claim 1, in an amount sufficient to stimulate the apoptosis in the cell.
14. (Original) The method of claim 13, wherein the cell is a cultured cell.
15. (Original) The method of claim 13, wherein the cell is disposed within a living organism.
16. (Original) The method of claim 15, wherein the organism is a mammal.
17. (Original) The method of claim 16, wherein the mammal is a human.
18. (Original) A compound that binds an Inhibitor of Apoptosis Protein (IAP) and relieves IAP-mediated inhibition of caspase activity, the compound having a formula R1-R2-R3-R4, wherein

R1 is A or a mimetic of A;

R2 is V, T or I, or a mimetic of V, T or I;

R3 is P or A, or a mimetic of P or A; and

R4 is F, Y, I or V, or a mimetic of F, Y, I or V.

19. (Original) The compound of claim 18, which is a non-peptide or partial peptide mimetic of an amino acid sequence selected from the group consisting of AVPI (SEQ ID NO:1), AVAF (SEQ ID NO:2); AIAY (SEQ ID NO:3), AVPF (SEQ ID NO:4), ATPF (SEQ ID NO:5), AVPY (SEQ ID NO:6) and ATPV (SEQ ID NO:7).

20. (Original) The compound of claim 19, which is a non-peptide or partial peptide mimetic of amino acid sequence AVPF (SEQ ID NO:4).

21. (Original) A compound that binds an Inhibitor of Apoptosis Protein (IAP) and relieves IAP-mediated inhibition of caspase activity, the compound having a formula R1-R2-R3-R4-R5-R6-R7, wherein

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R1 is A or a mimetic of A;
R2 is V, T or I, or a mimetic of V, T or I;
R3 is P or A, or a mimetic of P or A; and
R4 is F, Y, I or V, or a mimetic of F, Y, I or V;
R5 is missing, or is Y or F, or a mimetic of Y or F;
R6 is present only if R5 is present, and is L or I, or a mimetic of L or I;

and

R7 is present only if R5 and R6 are present, and is P or a mimetic of P.

22. (Original) The compound of claim 21, comprising a partial peptide or non-peptide mimetic of an amino acid sequence selected from the group consisting of AVAFYIP (SEQ ID NO:9), AIAYFLP (SEQ ID NO:10) and AVPFYLP (SEQ ID NO:11).

23. (Withdrawn) A method of making a drug suitable for treating cell proliferative disease in a mammal by promoting apoptosis in proliferatively diseased cells, the method comprising:

- a) constructing a compound that binds a mammalian IAP and relieves IAP-mediated inhibition of caspase activity, wherein the compound binds a surface groove within a BIR3 domain of the IAP; and
- b) determining whether the compound promotes apoptosis in a proliferatively diseased cell, an affirmative determination indicating that the drug is suitable for treating the cell proliferative disease.

24. (Withdrawn) The method of claim 23, wherein the cell proliferative disease is cancer.

25. (Withdrawn) The method of claim 23, wherein the compound constructed is a partial peptide or non-peptide mimetic of a tetrapeptide having an amino acid sequence the same as an N-terminal sequence of a cellular IAP-binding protein.

26. (Withdrawn) A method of screening for a compound that binds an IAP at a surface groove within a BIR domain, the method comprising:

- a) providing a synthetic tetrapeptide that binds a selected IAP and relieves IAP-mediated inhibition of caspase activity, wherein the tetrapeptide binds a surface groove within a BIR domain of the IAP;
- b) combining the tetrapeptide and the IAP in the presence of a test compound under conditions wherein, in the absence of the test compound, a pre-determined quantity of the tetrapeptide would bind the IAP; and

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c) determining if the quantity of the tetrapeptide bound to the IAP is decreased in the presence of the test compound, the decrease being indicative that the test compound binds the IAP and relieves IAP-mediated inhibition of caspase activity.

27. (Withdrawn) The method of claim 26, which further comprises the step of determining if the test compound modulates IAP-mediated inhibition of caspase activity.

28. (Withdrawn) The method of claim 27, wherein the modulating comprises relieving IAP-mediated inhibition of caspase activity.

29. (Withdrawn) The method of claim 27, wherein the modulating comprises promoting IAP-mediated inhibition of caspase activity.

30. (Withdrawn) The method of claim 26, which further comprises the step of determining if the test compound modulates cellular apoptosis.

31. (Withdrawn) The method of claim 30, wherein the modulating comprises promoting apoptosis.

32. (Withdrawn) The method of claim 30, wherein the modulating comprises inhibiting apoptosis.